Antiandrogen. I. 2-Azapregnane and 2-Oxapregnane Steroids

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2-Azachlormadinone acetate (5a, 17-acetoxy-6-chloro-2-azapregna-4,6-diene-3,20-dione), 2-oxachlormadinone acetate (6, 17-acetoxy-6-chloro-2-oxapregna-4,6-diene-3,20-dione) and the derivatives were prepared as potential antiandrogenic agents. Biological evaluation showed that 5a and 6 had a potent antiandrogenic activity when tested in the castrated male rat.

Keywords antiandrogen; ventral prostate; chlormadinone acetate; 2-azachlormadinone acetate; 2-oxachlormadinone acetate; osmium oxidation; reductive amination; ozonolysis; structure–activity relationship

Pappo and coworkers[1] reported the pioneering studies on the synthesis of 2-oxasteroids during the 1960s. While such a replacement is not expected to change the shape of the molecule, the chemical property of the carbonyl group at C_3 must be different from that of the normal steroids. In the binding of 2-oxa-4-en-3-one steroid[2] to the nuclear androgen receptor of rat ventral prostate, the binding affinity is similar to that of the parent steroid, suggesting that the carbonyl function of the lactone may bind to the receptor site behaving similarly to the normal ketone.

Chlormadinone acetate (**1**), well known as a potent antiandrogen,[3] has been used in clinical treating for prostatic hypertrophy and prostatic cancer. The antiandrogen has been reported to be metabolized to 2-hydroxylated compound or 3-hydrogenated compound in the rat and the human.[4] Incorporation of oxygen or nitrogen atom into the steroid nuclei at C_2 might affect the metabolism. This report describes the preparation and the antiandrogenic activity of 2-azachlormadinone acetate (17-acetoxy-6-chloro-2-azapregna-4,6-diene-3,20-dione, **5a**), 2-oxachlormadinone acetate (17-acetoxy-6-chloro-2-oxapregna-4,6-diene-3,20-dione, **6**) and the derivatives.

In our initial approach to the synthesis of 2-oxachlormadinone acetate (**6**), **1** was chosen as a starting material, which was readily dehydrogenated with dichlorodicyanobenzoquinone (DDQ) in dioxane to the trienone (**2**) in a good yield. Regioselective oxidation of **2** with osmium tetroxide[5] in the presence of periodic acid as a co-oxidant was performed to give the lactol (**3**) in a moderate yield.

Frimer *et al.*[6] reported that the 1α-isomer of the

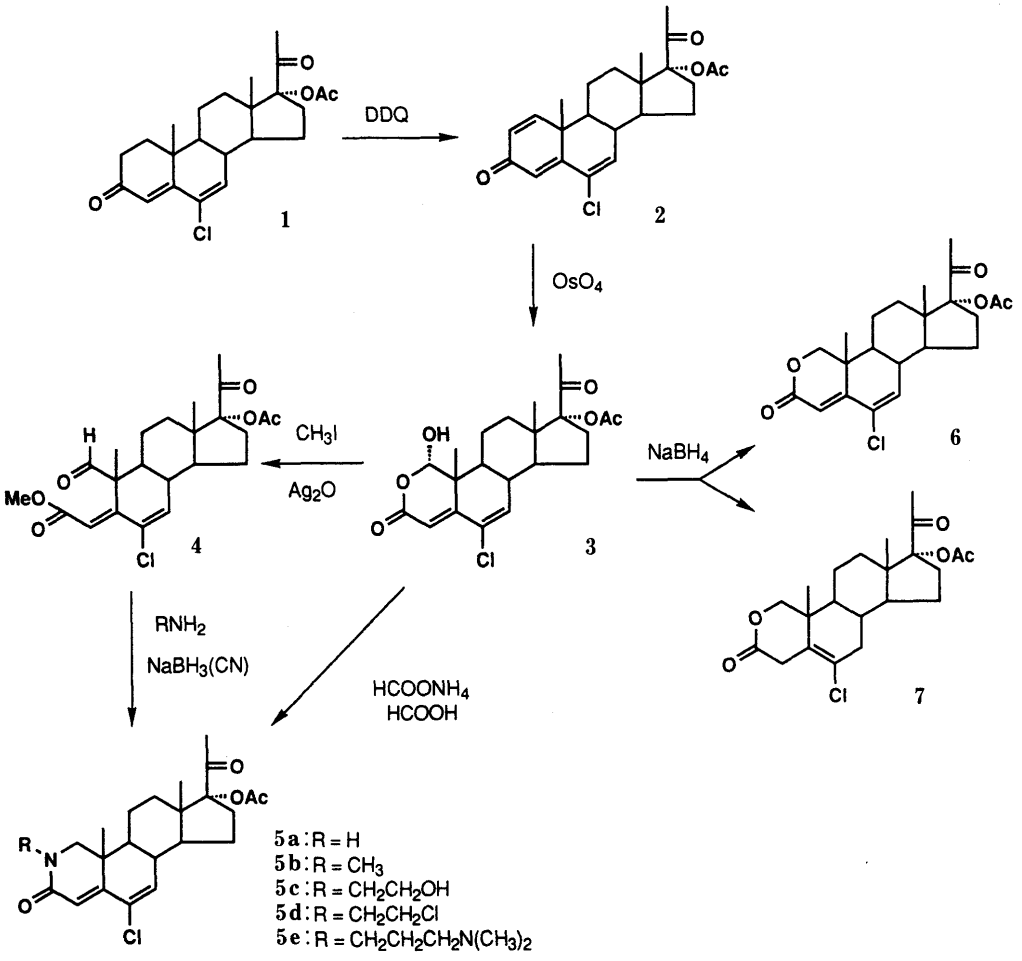

Chart 1

lactol prepared from 4-en-3-one steroid by autooxidation was thermodynamically more stable than the 1β-isomer ($\alpha:\beta=9:1$) and the chemical shift of the C_1-proton in the 1α-isomer was observed at lower field ($\Delta\delta=0.06$ ppm) in comparison with that in the 1β-isomer. In order to make sure of the structural assignment, **3** was treated with alkali to open the lactone ring, and then the product was acidified with diluted hydrochloric acid to the lactol. The nuclear magnetic resonance (NMR) spectrum of the recovered lactol showed no difference from that of **3**, in which the chemical shift of the C_1-proton appeared at 5.54 ppm as a singlet. Attempted isolation of the 1β-isomer from the above treatment resulted in failure because of its low yield. Then, a nuclear Overhauser effect (NOE) difference spectrum of **3** was obtained. When the methyl signal at C_{10} (δ 1.20) was irradiated, NOE was observed at signal due to the proton at C_1 (δ 5.54), suggesting the hydroxyl group at C_1 to be α-orientation.

Incorporation of a nitrogen atom into the steroid nuclei was accomplished by treatment[7] of **3** with ammonium formate and formic acid to furnish the lactam (**5a**) in 17% yield. As the yield was unsatisfactory, **3** was treated with methyl iodide in the presence of silver oxide[8] to afford the aldehyde (**4**), which was subjected to reductive amination[9] with ammonium acetate and sodium cyanoborohydride ($NaBH_3(CN)$) to give the lactam (**5a**) in 64% yield. In the latter case, several alkyl amines were used instead of ammonium acetate to give the corresponding lactam analogues (**5b**, **5c**, and **5e**), respectively, as shown in Chart 1.

Reduction of **3** with sodium borohydride in the usual manner gave 2-oxachlormadinone acetate (**6**), accompanied by 5-ene compound (**7**) as a byproduct generated *via* 1,6-addition reaction. In the reduction of **3** to **6**, it is interesting to know whether the inherent proton at C_1 of **3** is situated as α- or β-configuration in **6** obtained. Thus, **3** was reduced with sodium borodeuteride ($NaBD_4$) in the same procedure to afford the deuterated lactone. Its NMR spectrum showed the high field signal (4.11 ppm) for 1α-proton absent, indicating that the reduction reaction was highly stereoselective and the 1β-proton in **3** was retained at the 1β-position of **6**.

Our improved route for the preparation of **6** was shown in Chart 2. 17-Acetoxypregna-1,4,6-triene-3,20-dione (**8**) was chosen as a starting material, which was oxidized by 1.3 molar *m*-chloroperbenzoic acid (*m*-CPBA) to give the 6α,7α-epoxide (**9**) in a good yield as well as reported in the related case.[10] Ozonolysis[11] of **9** in pyridine at -30 °C afforded the lactol (**10**) in a good yield. In the NMR spectrum of **10**, the chemical shift of the C_1-proton was observed at 5.45 ppm as a singlet, showing a similar pattern to that of **3**. Reduction of **10** with sodium borohydride in the methanol–tetrahydrofuran (THF) mixture followed by treatment with concentrated hydrochloric acid gave the lactone (**11**) in a good yield. In the work-up, the mild neutralization of the reduction product with diluted sulfuric acid afforded the epoxy lactone (**12**).

Dehydration of **11** under the usual procedure[12] reported in the preparation of chlormadinone acetate from 6β-chloro-7α-hydroxy compound resulted in failure. Therefore, the lactone (**11**) was subjected to acetylation by acetic anhydride–pyridine mixture to give the acetate

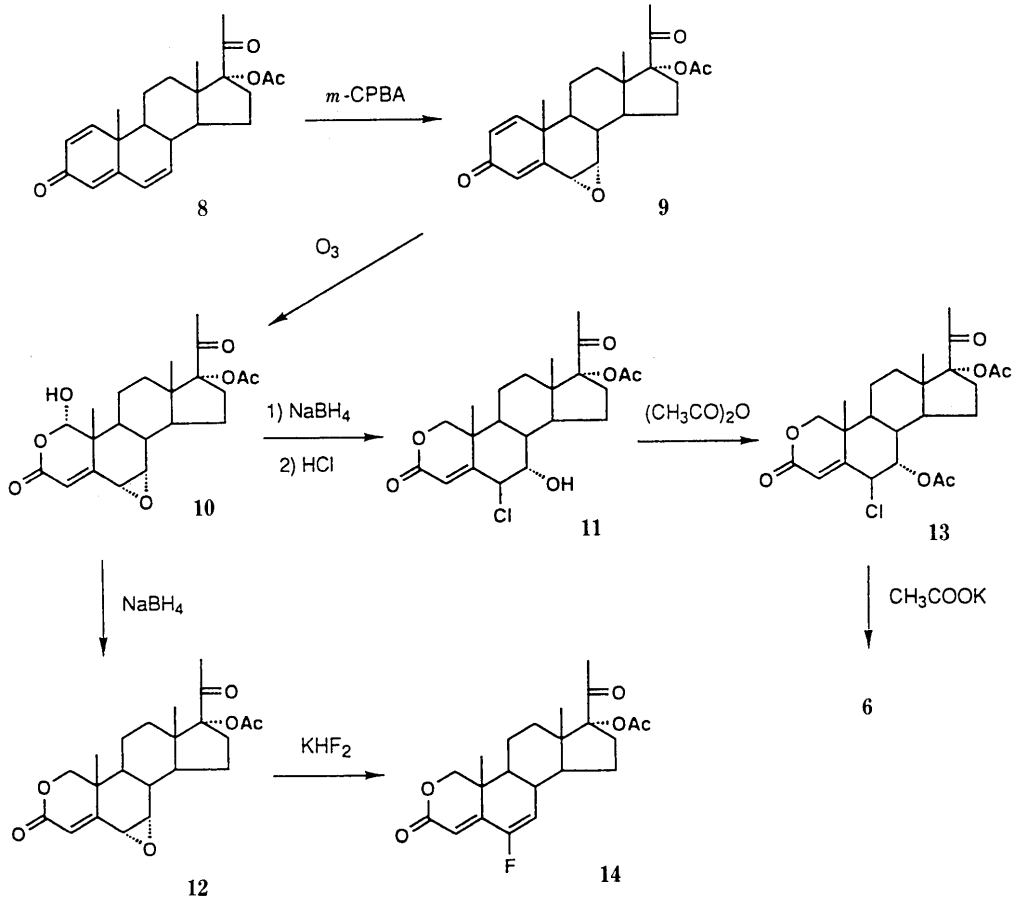

Chart 2

(**13**). Treatment of **13** with potassium acetate in *N*,*N*-dimethylformamide (DMF) at 70 °C furnished the desired compound, **6**, in a high yield.

A 6-fluoro compound (**14**) was also prepared according to the method reported in the normal steroid.[12] Treatment of the epoxide (**12**) with potassium hydrogenfluoride in dimethyl sulfoxide (DMSO) at 140 °C gave the desired compound, **14**, in a moderate yield.

The selective oxygenation of the trienone (**15**)[13] to a lactol failed in the same method described in **3** from **2**, because the 6,7-double bond seemed to be more reactive than the other double bonds. Therefore, it seemed to be the promising way that the 6,7-double bond was, at first, protected with an epoxy group, which was removed after construction of the A ring. Thus, the trienone (**15**) was converted to the epoxide (**16**) by treatment with *m*-CPBA. Compound (**16**) was subjected to ozonolysis to yield the lactol (**17**) in a good yield, of which NMR data at C_1-proton gave similar structural information as that of **3**. Reduction of **17** with sodium borohydride in the usual manner followed by deprotection of the epoxy function with diphosphorous tetraiodide[14] furnished the 2-oxa compound (**18**) of megestrol acetate.[13] Treatment of **17** with methyl iodide in the presence of silver oxide led to an aldehyde, which was converted to the lactam (**19**) by reductive amination as shown in the preparation of **5a**. Compound (**19**) led to the 6-methyl compound (**20**) by reduction with diphosphorus tetraiodide as described in the preparation of **18**.

Addition of difluorocarbene[15] into **6** gave only one product, 6α,7α-difluoromethylene (**21**) (Chart 4). On the other hand, the 4,6-diene (**22**), prepared from **12** by the diphosphorus tetraiodide reduction method, was converted to a mixture of α- and β-isomers in the same procedure, which was subjected to preparative thin-layer chromatography (TLC) to give the pure compounds, **23a** and **23b**, respectively. The chemical structures of both compounds were confirmed by NMR analysis, in analogy with the

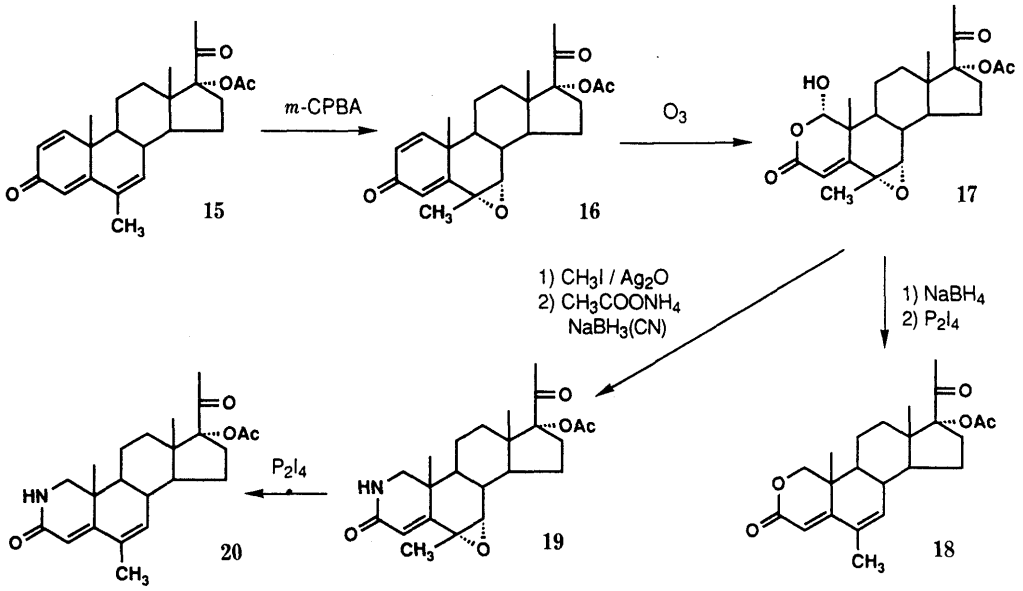

Chart 3

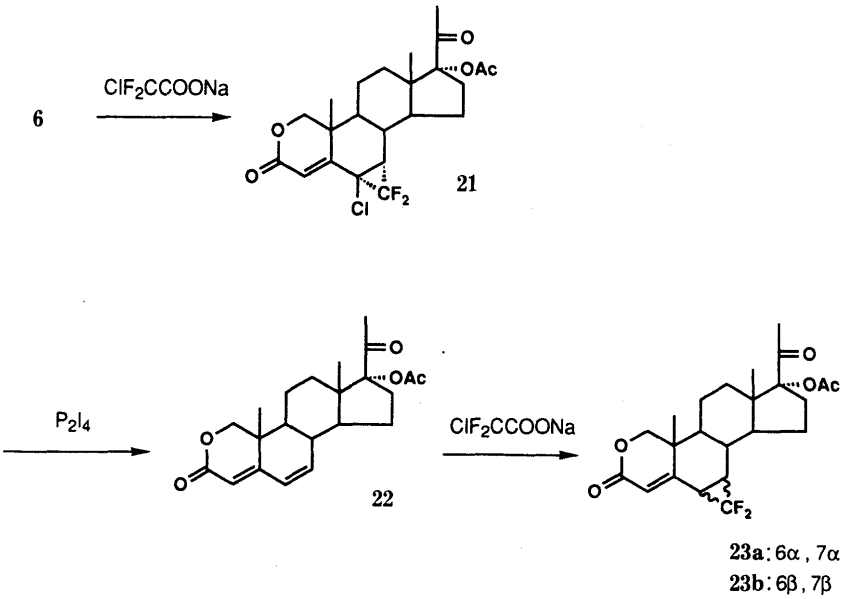

Chart 4

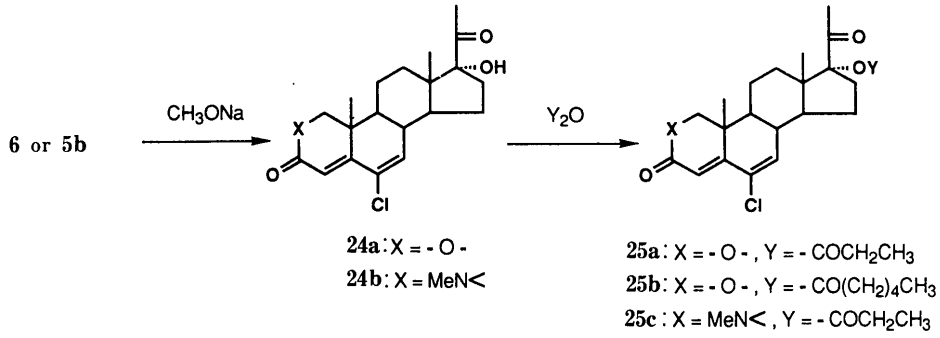

Chart 5

TABLE I. The Effect of 2-Oxapregnanes on Accessory Sex Organ Weights in Castrated Rat Given Testosterone Propionate (50 μg/rat, s.c.)

Compound	Dose (mg/kg)	Route[a]	Organ weight[b] (mg/100 g body weight)	
			Ventral prostate	Seminal vesicle
3	10	s.c.	21.8±2.6	27.8±2.7
6	0.67	*p.o.*	14.7±1.2	23.6±1.3
6	2	*p.o.*	12.1±0.6[c]	18.0±1.2[d]
6	6	*p.o.*	8.8±0.4[c]	9.6±0.7[c]
7	5	s.c.	12.7±1.7[e]	21.3±1.9
14	2.5	s.c.	21.2±2.3	30.9±2.3
18	10	s.c.	18.0±2.4	25.4±1.7
21	10	*p.o.*	15.7±1.8	24.2±2.5
22	5	s.c.	21.5±0.5	38.8±2.1[d]
23a	10	*p.o.*	22.7±2.7	28.1±3.5
23b	10	*p.o.*	23.2±1.5	38.1±1.9[d]
24a	2.5	s.c.	17.1±1.4	31.8±2.4
25a	2.5	s.c.	10.7±1.1[d]	18.6±2.3[e]
25b	10	s.c.	22.1±1.0	35.1±1.7[e]
CMA	5	*p.o.*	15.6±0.8[e]	25.2±0.8
CMA	15	*p.o.*	13.7±1.0[d]	22.0±1.3[e]
CMA	45	*p.o.*	10.6±0.4[c]	15.6±1.1[c]
Castrated control			5.4+0.2[c]	5.1±0.4[c]
T.P. control			18.8±1.2	27.3±2.1

a) *p.o.*: *per os*. s.c.: subcutaneous. *b*) Each value represents the mean±S.E. (n=4—10). *c*) Significantly different from the T.P. control ($p<0.001$). *d*) Significantly different from the T.P. control ($p<0.01$). *e*) Significantly different from the T.P. control ($p<0.05$). CMA: chlormadinone acetate. T.P.: testosterone propionate.

TABLE II. The Effect of 2-Azapregnanes on Accessory Sex Organ Weights in Castrated Rat Given Testosterone Propionate (50 μg/rat, s.c.)

Compound	Dose (mg/kg)	Route[a]	Organ weight[b] (mg/100 g body weight)	
			Ventral prostate	Seminal vesicle
5a	0.67	s.c.	19.3±1.4	32.2±1.2
5a	2	s.c.	15.2±0.5[c]	24.4±1.6[c]
5a	6	s.c.	8.5±1.1[d]	12.0±2.2[d]
5b	0.67	s.c.	19.3±0.7	31.3±0.8
5b	2	s.c.	17.8±0.9	27.6±1.3
5b	6	s.c.	12.3±1.0[e]	24.7±1.5[c]
5c	0.67	s.c.	21.5±1.2	34.1±3.3
5c	2	s.c.	24.7±0.8	36.9±1.9
5c	6	s.c.	22.3±3.2	36.7±4.5
5d	2.5	s.c.	23.3±1.3	39.1±2.5
5e	5	s.c.	25.5±4.4	36.5±3.6
20	2.5	s.c.	23.7±0.6	37.7±4.5
24b	2.5	s.c.	22.6±2.3	33.0±1.9
25c	5	s.c.	23.4±1.8	37.9±2.1
CMA	5	*p.o.*	15.8±1.0[c]	24.6±1.4[c]
CMA	15	*p.o.*	11.5±0.5[e]	16.0±0.7[e]
CMA	45	*p.o.*	8.7±0.8[d]	10.6±0.8[d]
Castrated control			4.7±0.5[d]	4.5±0.7[d]
T.P. control			22.5±2.4	31.7±2.1

a) *p.o.*: *per os*. s.c.: subcutaneous. *b*) Each value represents the mean±S.E. of 5 rats. *c*) Significantly different from the T.P. control ($p<0.05$). *d*) Significantly different from the T. P. control ($p<0.001$). *e*) Significantly different from the T.P. control ($p<0.01$). CMA: chlormadinone acetate. T.P.: testosterone propionate.

NMR data reported in 6,7-difluoromethylene compounds.[15]

The derivatives of 17-acyloxy compounds were synthesized for the effect of the substitution to the activity *via* the route shown in Chart 5. The acetates (**6** and **5b**) were treated with sodium methoxide in methanol to give the alcohols (**24a** and **24b**), respectively, in a good yield. The alcohols (**24a** and **24b**) were heated with propionic anhydride at 130 °C for 6 h to afford the propionates (**25a** and **25c**), respectively. In the same method, treatment of **24a** with caproic anhydride gave the caproate (**25b**).

Biological Activities The antiandrogenic activity of the compounds obtained was determined in immature castrated rats treated with testosterone propionate. The ability of the compounds to antagonize the androgen-stimulated weight gain of the seminal vesicle and ventral prostate were served as a measure of their activity.[16] These data are shown in Tables I and II.

The high antiandrogenic activity of 2-oxachlormadinone acetate (**6**) was observed. The potency was the highest in the steroidal antiandrogen, as judged from comparison with that of chlormadinone acetate. 2-Azachlormadinone acetate (**5a**) was also shown to be more active than chlormadinone acetate. Substitution of the chlorine atom at C_6 into a fluorine atom abolished the activity in the dose tested, against the results on the normal pregnane series.[14] A full biological evaluation of **6** will be reported elsewhere.

Experimental

Melting points were measured on a Mettler FPI melting point apparatus and are uncorrected. ^{1}H-NMR spectra were determined on a Hitachi R-90H instrument or a JEOL JNM GX-500 instrument in $CDCl_3$ solution using tetramethylsilane as an internal standard. Mass spectra (MS) were recorded on a Shimadzu GCMS-QP1000 spectrometer. Elemental analysis was performed on a Hitachi 026 CHN analyzer. Preparative TLC was carried out on 20×20 cm plates with 0.25 or 2 mm layer of Merck silica gel 60 GF 254. Ozone was generated with a Nippon ozone 0-10-2 instrument.

17-Acetoxy-6-chloropregna-1,4,6-triene-3,20-dione (2) A solution of **1** (50 g) and DDQ (40 g) in dioxane (625 ml) was refluxed for 3 h and then cooled. The mixture was concentrated to dryness and the residue was chromatographed on alumina column using CH_2Cl_2 as an eluent to give **2** (43.6 g, 87.6%). An analytical sample was obtained by recrystallization from Me_2CO as colorless prisms, mp 110—112 °C. *Anal.* Calcd for

$C_{23}H_{27}ClO_4$: C, 68.56; H, 6.75. Found: C, 68.65; H, 6.80. ^{1}H-NMR ($CDCl_3$) δ: 0.75 (3H, s), 1.24 (3H, s), 2.06 (3H, s), 2.07 (3H, s), 6.20 (1H, d, J=2 Hz), 6.31 (1H, dd, J=10, 2 Hz), 6.61 (1H, br s), 7.04 (1H, d, J=10 Hz). MS m/z: 402 (M^+), 360, 359, 342, 327, 299.

17-Acetoxy-6-chloro-1α-hydroxy-2-oxapregna-4,6-diene-3,20-dione (3) Oxidation of **2** with Osmium Tetroxide: To a solution of **2** (300 mg) and OsO_4 (10 mg) in dioxane (6 ml) was added a solution of $NaIO_4$ (670 mg) in water (2 ml) and the mixture was refluxed for 3 h. After addition of H_5IO_6 (320 mg), the mixture was refluxed for 30 min and poured into 5% $Na_2S_2O_3$. The product was extracted with EtOAc. The organic layer was washed with water, dried over anhydrous $MgSO_4$, and then concentrated to dryness. The crude product was subjected to preparative TLC ($CHCl_3$: Me_2CO = 9 : 1) to give **3** (144 mg, 45.7%). An analytical sample was obtained by recrystallization from Me_2CO–hexane as colorless prisms, mp 276—278 °C. *Anal.* Calcd for $C_{22}H_{27}ClO_6$: C, 62.48; H, 6.44. Found: C, 62.58; H, 6.37. ^{1}H-NMR ($CDCl_3$) δ: 0.72 (3H, s), 1.20 (3H, s), 2.06 (3H, s), 2.12 (3H, s), 5.54 (1H, s), 6.21 (1H, s), 6.35 (1H, br s). MS m/z: 422 (M^+), 380, 376, 362, 337, 319.

Oxidation of **2** with Ozone: A solution of **2** (200 mg) in CH_2Cl_2 (4 ml) and pyridine (4 ml) was treated by passing a stream of ozone (1.0 mmol/min, 5 min) at −78 °C. The progress of the reaction was followed by TLC analysis. The resulting mixture was stirred for 15 min at room temperature and poured into 10% $NaHSO_3$. The product was extracted with EtOAc. The organic layer was washed with 5% HCl, 5% $NaHCO_3$ and then water. The organic layer was dried over anhydrous $MgSO_4$ and concentrated to dryness. The crude product was subjected to preparative TLC ($CHCl_3$: Me_2CO = 9 : 1) to give **3** (32 mg, 15.2%).

Attempted Isomerization of 3 A solution of **3** (300 mg) in EtOAc (10 ml) and 2% NaOH (10 ml) was vigorously stirred for 5 min at 0 °C. From the organic layer, the starting material (**3**, 206 mg) was recovered. The aqueous layer was acidified with 3% HCl and the product was extracted with EtOAc. The organic layer was washed with water, dried over anhydrous $MgSO_4$, and concentrated to dryness to give a crystalline material (45 mg), of which NMR spectrum was identical with that of **3**.

Methyl 17-Acetoxy-6-chloro-1,20-dioxo-A-nor-1,2-secopregna-3,6-dien-2-oate (4) A mixture of **3** (1.75 g), Ag_2O (8.75 g) and methyl iodide (19 ml) was refluxed for 3 h. The precipitate was removed by filtration, and the filtrate was concentrated to dryness. The crude product was subjected to preparative TLC ($CHCl_3$) to give **4** (1.41 g, 80.0%). An analytical sample was obtained by recrystallization from Me_2CO–hexane as colorless prisms, mp 173—177 °C. *Anal.* Calcd for $C_{23}H_{29}ClO_6$: C, 63.23; H, 6.69. Found: C, 63.46; H, 6.58. ^{1}H-NMR ($CDCl_3$) δ: 0.71 (3H, s), 1.48 (3H, s), 2.02 (3H, s), 2.08 (3H, s), 3.68 (3H, s), 6.32 (1H, br s), 6.48 (1H, s), 9.57 (1H, s). MS m/z: 436 (M^+), 408, 401, 377, 373, 305.

17-Acetoxy-6-chloro-2-azapregna-4,6-diene-3,20-dione (5a) From **3**: A mixture of **3** (300 mg), ammonium formate (3.5 g) and formic acid (4 ml) was refluxed for 28 h. The mixture was diluted with water and the product was extracted with EtOAc. The organic layer was washed successively with 4% NaOH, 5% HCl, 5% $NaHCO_3$, and then water. The organic layer was dried over anhydrous $MgSO_4$ and concentrated to dryness. The crude product was subjected to preparative TLC ($CHCl_3$: Me_2CO = 6 : 1) to give **5a** (50 mg, 17.4%). An analytical sample was obtained by recrystallization from MeOH as colorless prisms, mp 287—288 °C. *Anal.* Calcd for $C_{22}H_{28}ClNO_4$: C, 65.10; H, 6.95; N, 3.45. Found: C, 65.25; H, 6.89; N, 3.32. ^{1}H-NMR ($CDCl_3$) δ: 0.71 (3H, s), 1.17 (3H, s), 2.06 (3H, s), 2.10 (3H, s), 3.27 (2H, m), 6.14 (1H, br s), 6.23 (1H, br s), 6.77 (1H, br s). MS m/z: 405 (M^+), 320, 302.

From **4**: To a solution of **4** (500 mg) in THF (5 ml) and MeOH (9 ml) were added ammonium acetate (1.3 g) and $NaBH_3(CN)$ (1.0 g). The mixture was stirred for 22 h at room temperature. After addition of 10% HCl (20 ml), the mixture was stirred for another 1 h. The product was extracted with $CHCl_3$. The organic layer was washed with 5% $NaHCO_3$ and then water, dried over anhydrous $MgSO_4$, and concentrated to dryness. The crude product was subjected to preparative TLC ($CHCl_3$: MeOH = 19 : 1) to give **5a** (295 mg, 63.5%).

17-Acetoxy-6-chloro-2-methyl-2-azapregna-4,6-diene-3,20-dione (5b) A mixture of **4** (600 mg), methylamine hydrochloride (225 mg), 30% methylamine in EtOH (0.75 ml), $NaBH_3(CN)$ (800 mg), THF (6 ml) and MeOH (6 ml) was stirred for 22 h at room temperature. The mixture was carried out as described for the preparation of **5a** from **4** to give **5b** (463 mg, 80.3%). An analytical sample was obtained by recrystallization from Me_2CO as colorless prisms, mp 293—294 °C. *Anal.* Calcd for $C_{23}H_{30}ClNO_4$: C, 65.78; H, 7.20; N, 3.34. Found: C, 65.83; H, 7.15; N, 3.30. ^{1}H-NMR ($CDCl_3$) δ: 0.71 (3H, s), 1.12 (3H, s), 2.06 (3H, s), 2.09 (3H, s), 3.20 (3H, s), 3.12 and 3.33 (2H, ABq, J=13 Hz), 6.13 (1H, s), 6.14 (1H, s). MS m/z: 419 (M^+), 359, 334, 316.

17-Acetoxy-6-chloro-2-(2-hydroxyethyl)-2-azapregna-4,6-diene-3,20-dione (5c) A mixture of **4** (500 mg), ethanolamine (733 mg), 26% HCl in 2-propanol (0.6 ml), $NaBH_3(CN)$ (300 mg), THF (5 ml) and MeOH (4.4 ml) was stirred for 22 h at room temperature. The mixture was carried out as described for the preparation of **5a** from **4** to give **5c** (333 mg, 64.7%). An analytical sample was obtained by recrystallization from Me_2CO as colorless prisms, mp 289—290 °C. *Anal.* Calcd for $C_{24}H_{32}ClNO_5$: C, 64.06; H, 7.17; N, 3.11. Found: C, 64.16; H, 7.12; N, 3.08. ^{1}H-NMR ($CDCl_3$) δ: 0.71 (3H, s), 1.13 (3H, s), 2.06 (3H, s), 2.10 (3H, s), 2.4—2.9 (4H, m), 3.26 and 3.55 (2H, ABq, J=13 Hz), 6.12 (1H, s), 6.18 (1H, s). MS m/z: 449 (M^+), 418, 346, 302.

17-Acetoxy-6-chloro-2-(2-chloroethyl)-2-azapregna-4,6-diene-3,20-dione (5d) To a solution of **5c** (100 mg) in $CHCl_3$ (3 ml) was added dropwise $SOCl_2$ (33 mg). The mixture was refluxed for 1 h. After addition of water, the product was extracted with $CHCl_3$. The organic layer was washed with 5% $NaHCO_3$ and then water, dried over anhydrous $MgSO_4$, and concentrated to dryness. The crude product was subjected to preparative TLC ($CHCl_3$: Me_2CO = 19 : 1) to give **5d** (21 mg, 20.2%), mp 198—203 °C. *Anal.* Calcd for $C_{24}H_{31}Cl_2NO_4$: C, 61.54; H, 6.67; N, 2.99. Found: C, 61.29; H, 6.57; N, 3.00. ^{1}H-NMR ($CDCl_3$) δ: 0.72 (3H, s), 1.18 (3H, s), 2.06 (3H, s), 2.10 (3H, s), 3.30 and 3.51 (2H, ABq, J=13 Hz), 3.73 (4H, br s), 6.15 (1H, s), 6.17 (1H, br s). MS m/z: 467 (M^+), 418, 407, 382, 364.

17-Acetoxy-6-chloro-2-(3-dimethylaminopropyl)-2-azapregna-4,6-diene-3,20-dione (5e) A mixture of **4** (64 mg), 3-dimethylaminopropylamine (194 mg), 26% HCl in 2-propanol (85 μl), $NaBH_3(CN)$ (40 mg), THF (0.6 ml) and MeOH (0.5 ml) was stirred for 15 h at room temperature. The mixture was carried out as described for the preparation of **5a** from **4** to give **5e** (37 mg, 51.4%), mp 132—134 °C. *Anal.* Calcd for $C_{27}H_{39}ClN_2O_4$: C, 66.04; H, 8.00; N, 5.70. Found: C, 66.27; H, 7.92; N, 5.67. ^{1}H-NMR ($CDCl_3$) δ: 0.71 (3H, s), 1.12 (3H, s), 2.06 (3H, s), 2.10 (3H, s), 2.26 (6H, s), 3.15 and 3.23 (2H, ABq, J=13 Hz), 3.0—3.6 (4H, m), 6.12 (1H, s), 6.14 (1H, br s). MS m/z: 490 (M^+), 475, 419, 72, 58.

17-Acetoxy-6-chloro-2-oxapregna-4,6-diene-3,20-dione (6) From **3**: To a solution of **3** (200 mg) in MeOH (13.4 ml) and THF (6.6 ml) was added a solution of $NaHCO_3$ (80 mg) and sodium acetate (2 g) in water (10 ml). After addition of $NaBH_4$ (72 mg), the mixture was stirred for 1 h at room temperature and acidified with conc. HCl. The product was extracted with EtOAc, and the organic layer was washed with water, dried over anhydrous $MgSO_4$, and then concentrated to dryness. The crude product was subjected to preparative TLC ($CHCl_3$: Me_2CO = 19 : 1) to give **6** (102 mg, 53.0%) from a polar fraction. An analytical sample was obtained by recrystallization with Me_2CO–hexane as colorless prisms, mp 253—255 °C. *Anal.* Calcd for $C_{22}H_{27}ClO_5$: C, 64.94; H, 6.69. Found: C, 64.90; H, 6.72. ^{1}H-NMR ($CDCl_3$) δ: 0.72 (3H, s), 1.21 (3H, s), 2.06 (3H, s), 2.09 (3H, s), 4.11 and 4.23 (2H, ABq, J=11 Hz), 6.19 (1H, s), 6.34 (1H, d, J=2 Hz). MS m/z: 406 (M^+), 363, 346, 321, 303.

From a less polar fraction, the hydrogenated product (**7**, 28 mg, 14.5%) was obtained, mp 150—155 °C. *Anal.* Calcd for $C_{22}H_{29}ClO_5$: C, 64.62; H, 7.15. Found: C, 64.77; H, 7.06. ^{1}H-NMR ($CDCl_3$) δ: 0.68 (3H, s), 1.15 (3H, s), 2.05 (3H, s), 2.11 (3H, s), 3.44 (2H, m), 3.95 and 4.20 (2H, ABq, J=11 Hz). MS m/z: 408 (M^+), 365, 348, 323, 305.

From **13**: A mixture of **13** (19.8 g), potassium acetate (990 mg) and DMF (79.2 ml) was stirred at 70 °C under N_2 for 5 h. The mixture was poured into water. The precipitate was collected by filtration, washed with water and dried. The crude product was recrystallized from CH_2Cl_2–MeOH to give **6** (14.5 g, 84.0%).

Reduction of 3 with $NaBD_4$ To a solution of **3** (200 mg) in MeOH (20 ml) was added a solution of $NaHCO_3$ (80 mg) and sodium acetate (2 g) in water (10 ml). After addition of $NaBD_4$ (80 mg, 97 atom%), the mixture was stirred for 1 h at room temperature. The mixture was worked up as above to give the deuterated **6** (156 mg, 80.7%). ^{1}H-NMR ($CDCl_3$) δ: 0.72 (3H, s), 1.21 (3H, s), 2.06 (3H, s), 2.09 (3H, s), 4.23 (1H, s), 6.19 (1H, s), 6.34 (1H, d, J=2 Hz). MS m/z: 407 (d_1, 92%), 406 (d_0, 8%).

17-Acetoxy-6α,7α-epoxypregna-1,4-diene-3,20-dione (9) To a solution of **8** (38.1 g) in $CHCl_3$ (110 ml) was added slowly *m*-CPBA (30.7 g), and the mixture was stirred for 20 h at room temperature. After addition of water, the organic layer was washed successively with 5% $NaHSO_3$, 5% Na_2CO_3 and water. The organic layer was dried over anhydrous $MgSO_4$ and concentrated to dryness. The crude product was recrystallized from Me_2CO to give **9** (27.7 g, 69.7%), mp 252—255 °C. *Anal.* Calcd for $C_{23}H_{28}O_5$: C, 71.85; H, 7.34. Found: C, 71.66; H, 7.29. ^{1}H-NMR ($CDCl_3$) δ: 0.73 (3H, s), 1.21 (3H, s), 2.05 (3H, s), 2.09 (3H, s), 3.38

(1H, br d, J=3.5 Hz), 3.67 (1H, d, J=3.5 Hz), 6.25 (1H, dd, J=2, 10 Hz), 6.48 (1H, d, J=2 Hz), 6.99 (1H, d, J=10 Hz). MS m/z: 384 (M^+), 341, 324, 309, 281.

The mother liquor was subjected to column chromatography on silica gel (Wakogel C-200) using $CHCl_3$–hexane (4:1) as an eluent and then to preparative TLC (benzene:EtOAc=4:1). Three by-products were obtained as follows.

17-Acetoxy-6β,7β-epoxypregna-1,4-diene-3,20-dione (5.2% yield): mp 110—114 °C. *Anal.* Calcd for $C_{23}H_{28}O_5$: C, 71.85; H, 7.34. Found: C, 71.68; H, 7.30. ^{1}H-NMR ($CDCl_3$) δ: 0.74 (3H, s), 1.32 (3H, s), 2.07 (3H, s), 2.08 (3H, s), 3.40 (1H, d, J=4 Hz), 3.58 (1H, d, J=4 Hz), 6.25 (1H, dd, J=2, 10 Hz), 6.49 (1H, d, J=2 Hz), 6.93 (1H, d, J=10 Hz). MS m/z: 384 (M^+), 341, 324, 281.

17-Acetoxy-1α,2α:6α,7α-diepoxypregn-4-ene-3,20-dione (2.7% yield): mp 228—232 °C. *Anal.* Calcd for $C_{23}H_{28}O_6$: C, 68.98; H, 7.05. Found: C, 69.05; H, 7.32. ^{1}H-NMR ($CDCl_3$) δ: 0.72 (3H, s), 1.16 (3H, s), 2.06 (3H, s), 2.12 (3H, s), 3.34 (1H, br d, J=3.7 Hz), 3.4—3.6 (3H, m), 6.12 (1H, d, J=1.5 Hz). MS m/z: 400 (M^+), 357, 340, 315, 297.

17-Acetoxy-4α,5α:6α,7α-diepoxypregn-1-ene-3,20-dione (2.4% yield): mp 248—253 °C. *Anal.* Calcd for $C_{23}H_{28}O_6$: C, 68.98; H, 7.05. Found: C, 68.74; H, 7.33. ^{1}H-NMR ($CDCl_3$) δ: 0.72 (3H, s), 1.24 (3H, s), 2.04 (3H, s), 2.10 (3H, s), 2.97 (1H, d, J=4 Hz), 3.33 (1H, br d, J=4 Hz), 3.53 (1H, d, J=2 Hz), 5.86 (1H, dd, J=2, 11 Hz), 6.35 (1H, d, J=11 Hz). MS m/z: 357 ($M^+ - COCH_3$), 340, 315, 297.

17-Acetoxy-6α,7α-epoxy-1α-hydroxy-2-oxapregn-4-ene-3,20-dione (10) A solution of **9** (19 g) in pyridine (85.8 ml) was treated by passing a stream of ozone (3.5 mmol/min, 1.5 h) at −30 °C. The progress of the reaction was followed by TLC. The resulting mixture was stirred for 30 min at room temperature. After addition of 10% $NaHSO_3$ (7.6 ml), the resulting mixture was stirred for 10 min and poured into a mixture of 7% H_2SO_4 (420 ml) and ice (190 g). The mixture was acidified with 20% H_2SO_4 (15 ml). The precipitate was collected by filtration, washed with water and dried to give **10** (16.9 g, 84.6%). An analytical sample was obtained by recrystallization from Me_2CO–hexane as colorless prisms, mp 245—249 °C. *Anal.* Calcd for $C_{22}H_{28}O_7$: C, 65.33; H, 6.98. Found: C, 65.40; H, 6.98. ^{1}H-NMR ($CDCl_3$) δ: 0.70 (3H, s), 1.17 (3H, s), 2.05 (3H, s), 2.13 (3H, s), 3.38 (1H, d, J=4 Hz), 3.53 (1H, d, J=4 Hz), 5.45 (1H, s), 6.18 (1H, s). MS m/z: 404 (M^+), 361, 344, 319, 301.

17-Acetoxy-6β-chloro-7α-hydroxy-2-oxapregn-4-ene-3,20-dione (11) To a solution of **10** (34.5 g) in THF (173 ml) and MeOH (128 ml) were added a solution of sodium acetate (12.2 g) in water (50 ml) and a solution of NaOH (2.2 g) in water (5 ml). After addition of $NaBH_4$ (2.5 g) and phenol (5.8 g), the mixture was stirred for 30 min at room temperature. Ice (100 g) and conc. HCl (124 ml) were added, and then the reaction mixture was stirred for 25 min at room temperature and poured into water. The precipitate was collected by filtration, washed with water and dried to give **11** (28.8 g, 79.5%). An analytical sample was obtained by recrystallization from Me_2CO–hexane as colorless prisms, mp 144—147 °C. *Anal.* Calcd for $C_{22}H_{29}ClO_6 \cdot 1/2H_2O$: C, 60.90; H, 6.97. Found: C, 60.65; H, 7.07. ^{1}H-NMR ($CDCl_3$) δ: 0.72 (3H, s), 1.46 (3H, s), 2.06 (3H, s), 2.11 (3H, s), 3.98 (1H, m), 4.09 and 4.22 (2H, ABq, J=11 Hz), 4.46 (1H, d, J=3 Hz), 6.00 (1H, s). MS m/z: 424 (M^+), 382, 381, 364, 339, 321, 303, 285.

17-Acetoxy-6α,7α-epoxy-2-oxapregn-4-ene-3,20-dione (12) This compound was prepared by using 5% H_2SO_4 instead of conc. HCl for the acidification process as described for the preparation of **11** in 85.2% yield. An analytical sample was obtained by recrystallization from Me_2CO–hexane as colorless prisms, mp 253—258 °C. *Anal.* Calcd for $C_{22}H_{28}O_6$: C, 68.02; H, 7.27. Found: C, 67.77; H, 7.29. ^{1}H-NMR ($CDCl_3$) δ: 0.70 (3H, s), 1.18 (3H, s), 2.05 (3H, s), 2.11 (3H, s), 3.48 (1H, d, J=4 Hz), 3.52 (1H, d, J=4 Hz), 4.11 (2H, m), 6.10 (1H, s). MS m/z: 388 (M^+), 345, 328, 303, 285.

7α,17-Diacetoxy-6β-chloro-2-oxapregn-4-ene-3,20-dione (13) To a mixture of **11** (23.4 g) and pyridine (13.4 ml) cooled in a water bath was added dropwise acetic anhydride (15.6 ml) with stirring, and the mixture was stirred for 18 h at room temperature. The resulting mixture was poured into water. The precipitate was collected by filtration, washed with water and then with ether, and dried. The crude product was recrystallized from CH_2Cl_2–MeOH to give **13** (19.8 g, 77.0%) as colorless prisms, mp 231—233 °C. *Anal.* Calcd for $C_{24}H_{31}ClO_7 \cdot 1/2CH_3OH$: C, 60.93; H, 6.89. Found: C, 60.65; H, 6.91. ^{1}H-NMR ($CDCl_3$) δ: 0.73 (3H, s), 1.49 (3H, s), 2.07 (3H, s), 2.10 (6H, s), 4.06 and 4.26 (2H, ABq, J=11 Hz), 4.50 (1H, d, J=2.5 Hz), 5.06 (1H, t, J=2.5 Hz), 5.95 (1H, s). MS m/z: 466 (M^+), 424, 406, 363, 321, 303.

17-Acetoxy-6-fluoro-2-oxapregna-4,6-diene-3,20-dione (14) A mixture of **12** (100 mg), KHF_2 (200 mg) and DMSO (1 ml) was heated at 140 °C with stirring for 20 min. After addition of water, the product was extracted with EtOAc. The organic layer was washed with 5% $NaHCO_3$ and water, dried over anhydrous $MgSO_4$, and concentrated to dryness. The crude product was subjected to preparative TLC ($CHCl_3$:Me_2CO=50:1) to give **14** (20 mg, 19.9%). *Anal.* Calcd for $C_{22}H_{27}FO_5$: C, 67.68; H, 6.97. Found: C, 67.62; H, 7.01. ^{1}H-NMR ($CDCl_3$) δ: 0.72 (3H, s), 1.22 (3H, s), 2.05 (3H, s), 2.09 (3H, s), 4.17 (2H, m), 5.70 (1H, br d, J=14 Hz), 5.96 (1H, s). MS m/z: 390 (M^+), 347, 330, 305, 287.

17-Acetoxy-6α,7α-epoxy-6β-methylpregna-1,4-diene-3,20-dione (16) A mixture of **15** (1.6 g), *m*-CPBA (1.7 g) and $CHCl_3$ (36 ml) was stirred for 6 h at room temperature. The mixture was diluted with water and the product was extracted with EtOAc. The organic layer was washed with 5% Na_2CO_3 and then water, dried over anhydrous $MgSO_4$, and concentrated to dryness. The crude product was subjected to preparative TLC (benzene:EtOAc=4:1) to give **16** (700 mg, 42.0%), mp 190—196 °C. *Anal.* Calcd for $C_{24}H_{30}O_5$: C, 72.34; H, 7.59. Found: C, 72.47; H, 7.51. ^{1}H-NMR ($CDCl_3$) δ: 0.73 (3H, s), 1.20 (3H, s), 1.57 (3H, s), 2.04 (3H, s), 2.07 (3H, s), 3.11 (1H, br s), 6.25 (1H, dd, J=2, 10 Hz), 6.56 (1H, d, J=2 Hz), 6.91 (1H, d, J=10 Hz). MS m/z: 398 (M^+), 355, 338, 323, 320, 313, 305, 295, 279, 277.

17-Acetoxy-6α,7α-epoxy-1α-hydroxy-6β-methyl-2-oxapregn-4-ene-3,20-dione (17) To a solution of **16** (2.18 g) in CH_2Cl_2 (40 ml) and pyridine (40 ml) was passed a stream of ozone (1.0 mmol/min, 1 h) at −78 °C. The progress of the reaction was followed by TLC analysis. The resulting mixture was stirred for 15 min at room temperature and poured into 10% $NaHSO_3$, and the product was extracted with $CHCl_3$. The organic layer was washed successively with 10% H_2SO_4, 5% $NaHCO_3$ and then water. The organic layer was dried over anhydrous $MgSO_4$ and concentrated to dryness. The crude product was subjected to preparative TLC ($CHCl_3$:Me_2CO=9:1) to give **17** (1.65 g, 72.1%), mp 283—285 °C. *Anal.* Calcd for $C_{23}H_{30}O_7$: C, 66.01; H, 7.23. Found: C, 66.20; H, 7.18. ^{1}H-NMR ($CDCl_3$) δ: 0.70 (3H, s), 1.17 (3H, s), 1.53 (3H, s), 2.05 (3H, s), 2.12 (3H, s), 3.12 (1H, s), 5.43 (1H, s), 6.24 (1H, s). MS m/z: 418 (M^+), 375, 358, 333, 315.

17-Acetoxy-6-methyl-2-oxapregna-4,6-diene-3,20-dione (18) To a solution of **17** (125 mg) in MeOH (7 ml) and THF (3 ml) was added a solution of $NaHCO_3$ (46 mg) and sodium acetate (1.23 g) in water (6 ml). After addition of $NaBH_4$ (48 mg), the mixture was stirred for 30 min at room temperature and acidified with 5% H_2SO_4. The product was extracted with EtOAc, and the organic layer was washed with water, dried over anhydrous $MgSO_4$, and concentrated to dryness to give a crude lactone (101 mg). A mixture of the lactone (200 mg), P_2I_4 (300 mg), pyridine (1.5 ml) and CH_2Cl_2 (6 ml) was refluxed for 6 h. The mixture was diluted with water, and the product was extracted with EtOAc. The organic layer was washed with 5% HCl, 5% $NaHSO_3$, 5% $NaHCO_3$ and water. The organic layer was dried over anhydrous $MgSO_4$, and concentrated to dryness. The crude product was subjected to preparative TLC ($CHCl_3$:Me_2CO=19:1) to give **18** (22 mg, 19.1%). *Anal.* Calcd for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82. Found: C, 71.57; H, 7.65. ^{1}H-NMR ($CDCl_3$) δ: 0.72 (3H, s), 1.16 (3H, s), 2.04 (3H, s), 2.08 (6H, s), 4.07 and 4.21 (2H, ABq, J=11 Hz), 5.72 (1H, s), 5.97 (1H, m). MS m/z: 386 (M^+), 344, 326, 301, 283.

17-Acetoxy-6α,7α-epoxy-6β-methyl-2-azapregn-4-ene-3,20-dione (19) A mixture of **17** (502 mg), Ag_2O (2 g) and methyl iodide (10 ml) was refluxed for 2 h. The mixture was worked up as described for the preparation of **4** to give an aldehyde (510 mg, 98.3%), mp 197—202 °C. *Anal.* Calcd for $C_{24}H_{32}O_7$: C, 66.65; H, 7.46. Found: C, 65.57; H, 7.58. ^{1}H-NMR ($CDCl_3$) δ: 0.69 (3H, s), 1.49 (3H, s), 1.53 (3H, s), 2.02 (3H, s), 2.09 (3H, s), 3.09 (1H, s), 3.67 (3H, s), 6.30 (1H, s), 9.44 (1H, s). MS m/z: 432 (M^+), 404, 329, 315, 311, 301, 283, 269.

A mixture of the aldehyde (102 mg) obtained above, ammonium acetate (300 mg), $NaBH_3(CN)$ (192 mg), THF (1 ml) and MeOH (2 ml) was stirred for 16 h at room temperature. After addition of water (3 ml), $CHCl_3$ (3 ml) and 10% H_2SO_4 (5 ml), successively, the mixture was stirred for 1 h, and the product was extracted with $CHCl_3$. The organic layer was washed with 5% $NaHCO_3$ and then water, dried over anhydrous $MgSO_4$, and concentrated to dryness. The crude product was subjected to preparative TLC ($CHCl_3$:MeOH=19:1) to give **19** (30 mg, 31.7%). *Anal.* Calcd for $C_{23}H_{31}NO_5$: C, 68.80; H, 7.78; N, 3.49. Found: C, 68.96; H, 7.64; N, 3.43. ^{1}H-NMR ($CDCl_3$) δ: 0.69 (3H, s), 1.08 (3H, s), 1.52 (3H, s), 2.04 (3H, s), 2.11 (3H, s), 3.09 (1H, s), 3.18 (2H, br s), 6.13 (1H, br s), 6.62 (1H, br s).

17-Acetoxy-6-methyl-2-azapregna-4,6-diene-3,20-dione (20) A mixture of **19** (25 mg), P_2I_4 (75 mg) and CH_2Cl_2 (1.5 ml) was stirred for 10 min

and diluted with 5% $NaHCO_3$. The product was extracted with $CHCl_3$. The organic layer was washed with water, dried over anhydrous $MgSO_4$, and concentrated to dryness. The crude product was subjected to preparative TLC ($CHCl_3$: MeOH = 19 : 1) to give **20** (15 mg, 62.5%), mp 259—264 °C. *Anal.* Calcd for $C_{23}H_{31}NO_4$: C, 71.66; H, 8.11; N, 3.63. Found: C, 71.79; H, 8.02; N, 3.70. ^{1}H-NMR ($CDCl_3$) δ: 0.71 (3H, s), 1.11 (3H, s), 1.86 (3H, br s), 2.06 (3H, s), 2.09 (3H, s), 3.19 and 3.26 (2H, ABq, J = 11 Hz), 5.69 (1H, br s), 5.86 (1H, br s), 6.32 (1H, br s). MS *m/z*: 385 (M^+), 325, 282.

17-Acetoxy-6β-chloro-6α,7α-difluoromethylene-2-oxapregn-4-ene-3,20-dione (21) A mixture of sodium chlorodifluoroacetate (3.4 g) in triglyme (17 ml) was added dropwise during 20 min to a boiling solution of **6** (525 mg) in triglyme (2 ml), and the mixture was refluxed for 30 min. The precipitate was removed by filtration, and the filtrate was concentrated to dryness. The product was extracted with diethyl ether, and the organic layer was washed with 5% $NaHCO_3$ and water, dried over anhydrous $MgSO_4$, and concentrated to dryness. The crude product was subjected to preparative TLC (benzene : EtOAc = 4 : 1) to give **21** (420 mg, 71.2%), mp 220—225 °C. *Anal.* Calcd for $C_{23}H_{27}ClF_2O_5$: C, 60.46; H, 5.96. Found: C, 60.27; H, 6.08. ^{1}H-NMR ($CDCl_3$) δ: 0.70 (3H, s), 1.29 (3H, s), 2.05 (3H, s), 2.12 (3H, s), 4.04 and 4.22 (2H, ABq, J = 11 Hz), 6.37 (1H, s). MS *m/z*: 456 (M^+), 414, 413, 371, 354, 353, 321, 303.

17-Acetoxy-2-oxapregna-4,6-diene-3,20-dione (22) A mixture of **12** (45 mg), P_2I_4 (100 mg) and CH_2Cl_2 (1.6 ml) was stirred for 10 min at room temperature, and diluted with 5% $NaHCO_3$. The product was extracted with EtOAc. The organic layer was washed with water, dried over anhydrous $MgSO_4$, and concentrated to give **22** (37 mg, 85.8%). An analytical sample was obtained by recrystallization from Me_2CO–hexane as colorless prisms, mp 244—248 °C. *Anal.* Calcd for $C_{22}H_{28}O_5$: C, 70.95; H, 7.58. Found: C, 70.84; H, 7.68. ^{1}H-NMR ($CDCl_3$) δ: 0.72 (3H, s), 1.18 (3H, s), 2.06 (3H, s), 2.10 (3H, s), 4.08 and 4.22 (2H, ABq, J = 11 Hz), 5.62 (1H, s), 6.17 (2H, s). MS *m/z*: 372 (M^+), 329, 312, 287, 269.

17-Acetoxy-6α,7α-difluoromethylene-2-oxapregn-4-ene-3,20-dione (23a) and 17-Acetoxy-6β,7β-difluoromethylene-2-oxapregn-4-ene-3,20-dione (23b) A mixture of sodium chlorodifluoroacetate (3 g) in triglyme (13 ml) was added dropwise during 20 min to a boiling solution of **22** (456 mg) in triglyme (3 ml), and the resulting mixture was refluxed for 30 min. The mixture was worked up as described for the preparation of **21** to give **23a** (286 mg, 55.3%) and **23b** (74 mg, 14.3%). **23a**: mp 243—247 °C. *Anal.* Calcd for $C_{23}H_{28}F_2O_5$: C, 65.39; H, 6.68. Found: C, 65.25; H, 6.75. ^{1}H-NMR ($CDCl_3$) δ: 0.68 (3H, s), 1.20 (3H, s), 2.04 (3H, s), 2.13 (3H, s), 4.04 and 4.18 (2H, ABq, J = 11 Hz), 5.95 (1H, s). MS *m/z*: 422 (M^+), 337, 319. **23b**: mp 237—241 °C. *Anal.* Calcd for $C_{23}H_{28}F_2O_5$: C, 65.39; H, 6.68. Found: C, 65.28; H, 6.79. ^{1}H-NMR ($CDCl_3$) δ: 0.68 (3H, s), 1.17 (3H, br s), 2.07 (3H, s), 2.11 (3H, s), 3.98 and 4.19 (2H, ABq, J = 10.5 Hz), 5.97 (1H, s). MS *m/z*: 422 (M^+), 379, 337, 319.

6-Chloro-17-hydroxy-2-oxapregna-4,6-diene-3,20-dione (24a) To a solution of **6** (116 mg) in THF (0.1 ml) and MeOH (5 ml) was added 30% sodium methoxide in MeOH (0.5 ml). The mixture was heated at 70 °C for 10 min and diluted with water. The product was extracted with EtOAc, and the organic layer was washed with 10% HCl, 5% $NaHCO_3$ and water, dried over anhydrous $MgSO_4$, and concentrated to dryness. The crude product was subjected to preparative TLC ($CHCl_3$: Me_2CO = 19 : 1) to give **24a** (70 mg, 67.3%). An analytical sample was obtained by recrystallization from Me_2CO–hexane as colorless prisms, mp 218—221 °C. *Anal.* Calcd for $C_{20}H_{25}ClO_4$: C, 65.84; H, 6.91. Found: C, 65.85; H, 6.78. ^{1}H-NMR ($CDCl_3$) δ: 0.75 (3H, s), 1.20 (3H, s), 2.24 (3H, s), 4.08 and 4.19 (2H, ABq, J = 13 Hz), 6.11 (1H, s), 6.34 (1H, br s). MS *m/z*: 364 (M^+), 321, 303.

6-Chloro-17-hydroxy-2-methyl-2-azapregna-4,6-diene-3,20-dione (24b) To a solution of **5b** (80 mg) in THF (3 ml) and MeOH (1 ml) was added 30% sodium methoxide in MeOH (0.5 ml). The mixture was worked up as described for the preparation of **24a**. The crude product was subjected to preparative TLC ($CHCl_3$: Me_2CO = 9 : 1) to give **24b** (55 mg, 76.8%), mp 138—143 °C. *Anal.* Calcd for $C_{21}H_{28}ClNO_3$: C, 66.74; H, 7.47; N, 3.71. Found: C, 66.86; H, 7.39; N, 3.75. ^{1}H-NMR ($CDCl_3$) δ: 0.77 (3H, s), 1.12 (3H, s), 2.27 (3H, s), 3.01 (3H, s), 3.17 and 3.33 (2H, ABq, J = 12 Hz), 6.12 (1H, s), 6.15 (1H, br s). MS *m/z*: 377 (M^+), 359, 334.

6-Chloro-17-propionyloxy-2-oxapregna-4,6-diene-3,20-dione (25a) A mixture of **24a** (70 mg) and propionic anhydride (2 ml) was heated at 130 °C for 6 h, and then cooled to room temperature. After addition of pyridine (2 ml) and water (2 ml), the mixture was stirred for 1 h at room temperature, and the product was extracted with EtOAc. The organic layer was washed with 10% HCl, 5% $NaHCO_3$ and water, dried over anhydrous $MgSO_4$, and concentrated to dryness. The crude product was subjected to preparative TLC ($CHCl_3$: Me_2CO = 19 : 1) to give **25a** (54 mg, 66.9%). An analytical sample was obtained by recrystallization from Me_2CO–hexane as colorless prisms, mp 199—202 °C. *Anal.* Calcd for $C_{23}H_{29}ClO_5$: C, 65.63; H, 6.94. Found: C, 65.72; H, 6.88. ^{1}H-NMR ($CDCl_3$) δ: 0.73 (3H, s), 1.17 (3H, t, J = 7 Hz), 1.22 (3H, s), 2.05 (3H, s), 2.38 (2H, q, J = 7 Hz), 4.11 and 4.22 (2H, ABq, J = 12 Hz), 6.17 (1H, s), 6.32 (1H, br s). MS *m/z*: 420 (M^+), 377, 346, 321, 303.

6-Chloro-17-hydroxy-2-oxapregna-4,6-diene-3,20-dione Caproate (25b) This compound was prepared as described for the preparation of **25a**, by using caproic anhydride instead of propionic anhydride as an acylating agent in 72.6% yield. An analytical sample was obtained by recrystallization from Me_2CO–ether as colorless prisms, mp 142—145 °C. *Anal.* Calcd for $C_{26}H_{35}ClO_5$: C, 67.45; H, 7.62. Found: C, 67.60; H, 7.73. ^{1}H-NMR ($CDCl_3$) δ: 0.73 (3H, s), 0.91 (3H, t, J = 6 Hz), 1.22 (3H, s), 2.05 (3H, s), 4.11 and 4.21 (2H, ABq, J = 11 Hz), 6.17 (1H, s), 6.32 (1H, br s). MS *m/z*: 462 (M^+), 321, 303.

6-Chloro-2-methyl-17-propionyloxy-2-azapregna-4,6-diene-3,20-dione (25c) This compound was prepared as described for the preparation of **25a**. The crude product was subjected to preparative TLC ($CHCl_3$: Me_2CO = 9 : 1) to give **25c** (14 mg, 70.5%), mp 270—280 °C. *Anal.* Calcd for $C_{24}H_{32}ClNO_4$: C, 66.43; H, 7.43; N, 3.23. Found: C, 66.23; H, 7.47; N, 3.26. ^{1}H-NMR ($CDCl_3$) δ: 0.71 (3H, s), 1.12 (3H, s), 1.17 (3H, t, J = 7 Hz), 2.05 (3H, s), 2.38 (2H, q, J = 7 Hz), 3.03 (3H, s), 3.12 and 3.33 (2H, ABq, J = 13 Hz), 6.13 (1H, s), 6.14 (1H, s). MS *m/z*: 433 (M^+), 390, 377, 359, 334, 316.

Antiandrogenic Assay Wistar strain male rats weighing 160—180 g were castrated at about 4 weeks of age. After two weeks' treatment, testosterone propionate (50 μg/rat) was administered daily by the subcutaneous route in 0.1 ml of sesame oil to all groups except the controls. The test compounds were given by the *per os* or the subcutaneous route daily for 5 days. On day 6, the animals were sacrificed, and seminal vesicles and ventral prostates were secured and weighed.

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